REMARKS

Claims 1-6 are pending in the present application. Claims 7 and 8 were previously withdrawn from consideration as drawn to a non-elected invention. By this amendment, claims 1-3 are amended, and claims 9-12 are added. Support for new claims 9-11 is found in the specification, *inter alia*, on pages 9 and 10, paragraph [0026], pages 25 and 26, paragraph [0074], and pages 66-69, Example 1. Support for new claim 12 is found in the specification, *inter alia*, on pages 71 and 72, Example 4. Accordingly, claims 1-6 and 9-12 are currently under consideration. No new matter has been added.

With respect to all claim amendments, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in a future continuation and/or divisional application.

Information Disclosure Statement

Applicants thank the Examiner for having considered the references previously submitted in the Information Disclosure Statements. Applicants note that the Examiner has not initialed reference no. 37-43 and 104-122 in the Information Disclosure Statement submitted September 6, 2006. Applicants would appreciate the Examiner initialing these references.

Objections to the Specification

A. The Examiner objects to the specification, alleging that the title is not indicative of the claimed invention. The Examiner suggested changing the title to: "METHODS FOR TREATING POST-SURGICAL PAIN BY ADMINISTERING AN ANTI-NERVE GROWTH FACTOR ANTAGONIST."

In response, Applicants have replaced the title with the one that the Examiner suggested. Accordingly, this objection should be withdrawn.

B. The Examiner also objects to the specification by alleging that it contains embedded hyperlinks and/or other form of browser-executable code.

In response, Applicants have amended the specification to change the embedded hyperlink "http://www.rna-tec.com/repair.htm" on page 43 into "the World Wide Web at rna-tec.com/repair.htm." A similar amendment was made to delete the embedded hyperlinks on page 44. Applicants believe these amendments should address the Examiner's concerns. Applicants have not found any other embedded hyperlinks or browser-executable code in the specification. Applicants respectfully request that this objection be withdrawn.

35 U.S.C. §112, second paragraph

Claims 1-7 stand rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 1 stands rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite because the claim does not have a step that clearly relates back to the preamble.

Applicants disagree with the Examiner. Applicants note that the treatment of post-surgical pain in the individual is achieved by administering an effective amount of the NGF antagonist; and therefore, a step indicating the treatment of post-surgical pain is not required. However, in the interest of expediting the prosecution, Applicants have amended claim 1 to recite "whereby the post-surgical pain in the individual is treated." This clause relates to the preamble, which should address the Examiner's concern. Accordingly, Applicants respectfully request that this rejection be withdrawn.

B. The Examiner rejected claims 2 and 3 under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for reciting the phrase "suppressed or ameliorated."

Applicants respectfully submit that the terms "ameliorated" as well as "suppressed" are clear to those skilled in the art, and this fulfills the requirement for definiteness. However, without acquiescence to the rejection, Applicants have amended claims 2 and 3 to delete the term "suppressed." The specification provides an unambiguous definition of the term "ameliorated." *See* page 22, paragraph [0063]. As stated in the specification, the term "ameliorating" post-surgical pain means a lessening or improvement of one or more symptoms of a post surgical pain, as compared to not administering an NGF antagonist, and the term "ameliorating" also includes shortening or reduction in duration of a symptom. Withdrawal of this rejection is respectfully requested.

C. Claim 2 stands further rejected under 35 U.S.C. 112, second paragraph, as allegedly lacking sufficient antecedent basis for the term "wherein resting pain."

In response, Applicants amended claim 2 to specify that "the post-surgical pain comprises resting pain" and that "the resting pain is ameliorated." In view of this amendment, Applicants respectfully request that this rejection be withdrawn.

D. Claim 3 stands further rejected under 35 U.S.C. 112, second paragraph, as allegedly lacking sufficient antecedent basis for the term "wherein mechanically-induced pain."

In response, Applicants amended claim 3 to specify that "the post-surgical pain comprises mechanically-induced pain" and that "the mechanically-induced pain is ameliorated." Accordingly, Applicants respectfully request that this rejection be withdrawn.

E. Claims 2 and 3 also stand rejected under 35 U.S.C. 112, second paragraph, as being allegedly indefinite for recited the phrases "resting pain" and "mechanically-induced pain," respectively. As noted by the Examiner, the specification defines "resting pain" as "pain occurring even while the individual is at rest as opposed to, for example, pain occurring when the individual moves or is subjected to other mechanical stimuli (for example, poking or prodding)." Page 24, paragraph [0069]. The specification also defines "mechanically-induced pain" as "pain induced by a mechanical stimulus, such as the application of weight to a surface, tactile stimulus, and stimulation caused or associated with movement (including coughing, shifting of weight, etc.)."

Page 24, paragraph [0070]. However, the Examiner asserts that pain associated with weight bearing, which was used by Applicants as a measure of resting pain, is actually pain involving "a mechanical stimulus, i.e., weight bearing." The Examiner further states that it is unclear what is encompassed by the phrase "resting pain" or "mechanically-induced pain."

Applicants respectfully submit that the terms "resting pain" and "mechanically-induced pain" are clear to those skilled in the art and thus satisfy the requirement for definiteness. For example, the specification clearly distinguishes these two types of pain: "[p]ost-surgical pain can have two clinically important aspects, namely resting pain, or pain that occurs when the patient is not moving and mechanical pain which is exacerbated by movement (coughing/sneezing, getting out of bed, physiotherapy, etc.)." Pages 4 and 5, paragraph [0010].

As described in the specification, the amount of weight bearing *while at rest* can be used as a measurement for *resting pain*. *See* page 67, paragraph [0171]. This test measures the willingness of an animal to bear weight on a limb while at rest. Here, the animal is applying its body weight to a surface. In contrast, some tests for mechanically-induced pain involve the *application of a mechanical stimulus to part of the animal's body*. For example, the specification teaches that as an exemplary measurement of mechanically-induced pain "tactile allodynia was tested by touching the skin, medial and proximal to the entry point of the incision, on the heel of the animal's hind paw with von Frey hairs in ascending order of force until a paw-withdrawal response was elicited." Pages 67 and 68, paragraph [0172]. Another example of *mechanically-induced pain* is pain that is exacerbated by *movement*. In view of these clarifying remarks, withdrawal of this rejection is respectfully requested.

F. Claim 3 also stands rejected under 35 U.S.C. 112, second paragraph, as allegedly being incomplete for omitting essential steps, such omission amounting to a gap between steps.

In response, Applicants note that mechanical-induced pain includes, for example, pain "which is exacerbated by movement (coughing/sneezing, getting out of bed, physiotherapy, etc.)." Page 5, paragraph [0010]. Thus, a post-surgical patient may have pain in the absence of movement

that is exacerbated by movement and thus is a type of mechanical-induced pain. Alternatively, a patient may have mechanical-induced pain that is generated by patient's movement. In both of these cases, a separate step of mechanically inducing the pain is not required since the patient may have the pain generated by patient's own movement, for example, exacerbated by movement or generated by movement. Thus, the step of mechanically inducing pain is not an essential step for treating the pain. Accordingly, withdrawal of this rejection is respectfully requested.

G. Claims 4-6 stand rejected for depending from an allegedly indefinite claim. In view of the amendments to claims 1-3, claims 1-3 and the claims that depend from them recite distinct subject matter. Accordingly, this rejection of claims 4-6 should be withdrawn.

In view of the above, Applicants respectfully request that the rejections under 35 U.S.C. §112, second paragraph, be withdrawn.

Claims Rejected Under 35 U.S.C. § 103

A. Claims 1-3 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Owolabi *et al.* (*J. Pharmacol. Exp. Ther.*, 289(3); 1271-1276, 1999) in view of Brennan, T.J. (*ILAR*, 40(3): 129-136, 1999). The Examiner states that Owolabi *et al.* teach that the administration of the ALE-0540 NGF receptor antagonist produces antiallodynia in a rat model of neuropathic pain and blocks tactile allogynia in rat model of inflammatory pain. The Examiner further states that Brennan teaches that post-surgical pain likely involves nerve injury, inflammation, pH changes, and central nervous system plasticity. Based on these documents, the Examiner alleges that the claimed invention is obvious over Owolabi *et al.* in view of Brennan because it would have been obvious to combine the references and one skilled in the art would have been motivated to administer ALE-0540 for post-surgical pain and would have had expected success from this treatment.

Applicants respectfully traverse this rejection.

To establish a *prima facie* case of obviousness, there must be some suggestion, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to

modify the reference or to combine reference teachings. MPEP §2143.01. Additionally, there must be a reasonable expectation of success. MPEP §2143.02.

Claims 1-3 are directed to a method for treating post-surgical pain by administering to an individual an effective amount of an NGF antagonist, whereby the post-surgical pain in the individual is treated.

Applicants submit that neither the cited references nor the general knowledge of one skilled in the art teach or suggest the use of an NGF antagonist for the specific treatment of post-surgical pain. The Examiner states that Owolabi *et al.* teach the treatment of neuropathic and inflammatory pain. As discussed in Applicants' specification, post-surgical pain involves different mechanisms than inflammatory or neuropathic pain and a therapy for inflammation (NAALADase) did not attenuate post-surgical pain:

> The different mechanisms involved in surgical or injury-induced pain as compared to inflammation is exemplified by the varying pharmacology and underlying anatomical substrates of pain relief in the two conditions. Yamamoto, *et al.*, (*Brian Res.* 909(1-2):138-144 (2001)) have shown that inhibition of spinal N-acetyl-alpha-linked acidic dipeptidase (NAALADase) causes a marked attenuation of mechanical pain which accompanies the inflammatory stimulus of carrageenan injection. However, in parallel experiments where NAALADase was inhibited in an identical fashion after an incision, there was no attenuation of mechanical pain. *These observations demonstrate that the biochemistry or pharmacology underlying post-surgical pain is distinct from those underlying inflammatory pain.* The anatomical structures important in modulating pain sensation have also been examined in post-surgical and other pain states (Pogatzki, *et al.*, *Anesthesiology*, 96(5):1153-1160 (May 2002)). Descending influences for the brainstem, more specifically the rostral medial medulla, are important modulators of secondary hyperalgesia in general inflammatory, neuropathic and visceral pain states. When the brain stem area was lesioned, no change in any pain response measured after incision was observed. These results indicate that primary and secondary hyperalgesia after an incision are not modulated by descending influence from the RMM. *The lack of contribution of descending facilitatory influences from the RMM to secondary hyperalgesia after gastrocnemius incision supports the notion that incision-induced pain involved dissimilar mechanisms compared with inflammatory and neuropathic pain.* In addition to the obvious differences in post-surgical or injury-induced pain from inflammatory, visceral or neuropathic pain, these results demonstrate that *the mechanisms involved in post-surgical pain (or injury-induced pain) are clearly different from other pains.*

Pages 6 and 7, paragraph [0014] (emphasis added).

Based on these substantial differences between post-surgical pain and both inflammatory and neuropathic pain, there was no motivation to use an agent that reduces inflammatory or neuropathic pain for the much different use of treating post-surgical pain. For example, Applicants' specification teaches that "the utility of a particular pharmacological (or other) intervention in treating post-surgical pain is not predictable by testing that pharmacological agent or intervention in inflammatory, visceral or neuropathic pain models." Page 7, paragraph [0014].

Rather than motivating a skilled artisan to arrive at the claimed invention, Brennan teaches away from the concept of using a compound (such as an NGF antagonist) that is allegedly useful for the treatment of inflammatory or neuropathic pain in methods for the treatment of post-surgical pain. For example, Brennan teaches:

> A surgical incision produces tissue injury that is distinctly different from chemical irritation with formalin, inflammation by carrageenan injection, or nerve injury by ligation. First, few models utilize a surgical incision as the noxious event. . . . The mechanisms for initiation and maintenance of pain after incision likely involve a combination of nerve injury, inflammation, pH changes, and central nervous system plasticity; *however, it must be emphasized that the contribution of each of these components is not known.* Perhaps a specific antiinflammatory agent may prevent the development of inflammation-induced hyperalgesia; *little or no effect may be observed in an incision model.* Because the etiology of incisional pain may be different from inflammatory pain, chemical irritation, or nerve injury, *the responses to treatment inhibiting the development and maintenance of pain behaviors may also differ.*

Page 133, second paragraph (emphasis added).

Brennan also indicates that the time scale of post-surgical pain differs from that of models for other types of pain, further suggesting that compounds that are useful in animal models for other types of pain may not be useful for post-surgical pain.

> The onset, progression, and duration of persistent pain behaviors in animal models of chemical irritation, inflammation and nerve injury, and pain and hyperalgesia in post-operative patients are different. In the plantar incision model, the incision and closure require 15 min to perform. Hyperalgesia is profound immediately after surgery and on the

> first postoperative day, gradually decreases but persists for about 5 days, and then is similar to sham and preoperative levels. The onset of pain in other animal models varies from minutes after injection of formalin, to hours after injection of inflammatory agents, or to days after nerve injury. This incisional model in the rat with quantifiable pain behaviors occurs on a time scale similar to most postoperative patients whose pain reports and mechanical hyperalgesia are usually the greatest immediately after surgery, serve for several days later, and then gradually diminish over 7 to 10 days.

Page 134, second paragraph.

Given this unpredictability in the utility of agents for inflammatory or neuropathic pain to also treat post-surgical pain, one skilled in the art would not have been motivated to use an NGF antagonist for the treatment of post-surgical pain. On this ground, the obviousness rejection may be properly withdrawn.

Additionally, a *prima facie* case of obviousness has not been established because there would not have been a reasonable expectation of success. As discussed above, Brennan discloses that post-surgical pain has different mechanisms of action and different time scales from inflammatory and neuropathic pain. Thus, a skilled artisan would not have had a reasonable expectation of success that an NGF antagonist would also be useful for the treatment of post-surgical pain. Additionally, Applicants' specification notes that resting pain and mechanically-induced pain may involve different mechanisms:

> Disappearance of pain at rest and persistence of pain with activities and in response to mechanical stimuli at the wound site is also present in patients after surgery. (Moiniche, et al., Acta Anaesthesiol. Scand. 41:785-9 (1997)). *Studies suggest that pain at rest and evoked pain caused by incisions are likely transmitted by different afferent fiber populations and/or different receptors.* Other than using local anesthetics to inhibit these evoked responses, few drugs that markedly reduce pain with coughing and movement after surgery are available.

Page 7, paragraph [0015] (emphasis added).

Thus, one skilled in the art would not have had a reasonable expectation that an NGF antagonist would successfully treat multiple components of post-surgical pain (*e.g.*, resting pain, mechanically-

induced pain, and thermal hyperalgesia), as discovered by Applicants (*see, e.g.*, pages 66-69, Example 1). On this ground, the obviousness rejection may be properly withdrawn.

In view of the above, the Examiner has not set forth a *prima facie* case for obviousness for claims 1-3. Applicants respectfully request that this rejection be withdrawn.

B. Claims 1-6 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Owolabi *et al.* (*J. Pharmacol. Exp. Ther.*, 289(3); 1271-1276, 1999) in view of Brennan, T.J. (ILAR 40(3): 129-136, 1999), and further in view of Knüsel *et al.* (*J. Neurochem.*, 59(6): 1987-1996, 1992). The Examiner states that Knüsel *et al.* teach that the kinase inhibitor K252a inhibits NGF. The Examiner alleges that a skilled artisan would have been motivated to use the kinase inhibitor K252a taught by Knüsel *et al.* to teat post-surgical pain because surgery is known to cause pain and would have had an expectation of success because ALE-0540, which would inherently inhibit the downstream kinase signaling associated with TrkA receptor activity, alleviates neuropathic pain and inflammatory pain.

Applicants respectfully traverse this rejection.

As discussed above, Owolabi *et al.* and Brennan (either alone or in combination) do not teach or suggest the administration of an NGF antagonist for post-surgical pain. One skilled in the art would also not have had a reasonable expectation of success that an NGF antagonist would be useful for treating surgical pain, which the prior art taught was distinctly different than other types of pain. Knüsel *et al.* do not provide any additional suggestions for the use of an NGF antagonist for the specific treatment of surgical pain. Knüsel *et al.* teach the inhibition of NGF with K252a but does not disclose or suggest the treatment of post-surgical pain. Therefore, one skilled in the art would not have had the required motivation or reasonable expectation of success for the administration of an NGF antagonist for post-surgical pain.

In view of the above, the Examiner has not established a *prima facie* case of obviousness. Applicants respectfully request that this rejection be withdrawn.

Double Patenting Rejection

Claims 1-3 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-3 of copending Application No. 10/682,638.

Applicants respectfully request that this rejection be held in abeyance until the Office has made a determination of allowable claims in the present application or in copending App. Ser. No. 10/682,638, at which time Applicants will address this issue.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 514712000400. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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